Tubulointerstitial Nephritis and Uveitis Syndrome: A Systematic Review

Síndrome de Nefrite Túbulo-Intersticial: Revisão Sistemática

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Recebido/Received: 2022-04-11 | **Aceite/Accepted:** 2022-08-07 | **Publicado/Published:** 2022-09-30

DOI: https://doi.org/10.48560/rspo.26970

ABSTRACT

INTRODUCTION: Tubulointerstitial nephritis and uveitis syndrome is a rare disease characterized by the occurrence of tubulointerstitial nephritis and uveitis, in the absence of other explainable systemic disease. In this review we aim to appraise and to clarify what is acknowledged in order to elucidate the demographics, genetic predisposition, most frequent symptoms and laboratory findings, most adequate treatment and also patient's prognosis.

METHODS: A systematic review across PubMed, Web of Science and Scopus was performed, according to PRISMA guidelines, in order to identify all relevant articles regarding both tubulointerstitial nephritis and uveitis.

RESULTS: We identified 240 publications, of which 176 were excluded. The average age of Tubulointerstitial nephritis and uveitis syndrome diagnosis was 30.6 years-old, with a female predominance (2:1); according to presentation symptoms, tubulointerstitial nephritis precedes uveitis more commonly and amongst uveitis cases the majority were bilateral anterior uveitis. Moreover, the most common systemic symptoms were fatigue, fever, and weight loss; blood analysis commonly presented with elevated serum creatinine, erythrocyte sedimentation rate, C-reactive protein, blood urea nitrogen level and urinalysis frequently showed proteinuria, glycosuria, and elevated urinary-β2-microglobulin. The majority (78.8%) of patients were putted on corticosteroids, with 21.9% needing an additional immunosuppressor, being mycophenolate mofetil (29.8%) and azathioprine (28.0%) the preferred ones. The mean time until relapse, which occurred in 48.3% of patients, was 89.3 days.

CONCLUSION: Tubulointerstitial nephritis and uveitis syndrome is not just a pediatric syndrome, as once thought. Presentation seems to be variable, although tubulointerstitial nephritis typically presents first, with systemic symptoms such as fatigue. As clinicians becomes more aware of the disease, follow-up after the first symptoms allows for earlier diagnosis. Relatively to treatment, most patients responded to corticosteroids, and despite the relapses, the prognosis was generally favorable.

KEYWORDS: Nephritis, Interstitial; Syndrome; Uveitis.

RESUMO

INTRODUÇÃO: A síndrome de nefrite e uveíte túbulo-intersticial é uma doença rara caracterizada pela ocorrência de nefrite túbulo-intersticial e uveíte, na ausência de outra doença sistêmica explicável. Nesta revisão pretendemos avaliar e esclarecer o que é reconhecido para elucidar os dados demográficos, a predisposição genética, os sintomas e achados laboratoriais mais frequentes, o tratamento mais adequado e também o prognóstico do paciente.

MÉTODOS: Foi realizada uma revisão sistemática na PubMed, Web of Science e Scopus, de acordo com as diretrizes PRISMA, de forma a identificar todos os artigos relevantes sobre nefrite túbulo-intersticial e uveíte.

RESULTADOS: Identificamos 240 publicações, das quais 176 foram excluídas. A idade média do diagnóstico da síndrome de nefrite e uveíte túbulo-intersticial foi de 30,6 anos, com predomínio do sexo feminino (2:1); De acordo com a apresentação, a nefrite túbulo-intersticial precede os sintomas de uveíte mais comumente e entre os casos de uveíte a maioria foi de uveíte anterior bilateral. Além disso, os sintomas sistêmicos mais comuns foram fadiga, febre e perda de peso; as análises sanguíneas comumente apresentaram elevação da creatinina sérica, da velocidade de hemossedimentação, da proteína C reativa, e do nível de nitrogênio ureico no sangue, na avaliação urinária frequentemente apresentaram proteinúria, glicosúria e a β2-microglobulina urinária elevada. A maioria (78,8%) dos pacientes recebeu corticoide, sendo que 21,9% necessitaram de um imunossupressor adicional, sendo o micofenolato de mofetil (29,8%) e a azatioprina (28,0%) os preferidos. O tempo médio até a recidiva, que ocorreu em 48,3% dos pacientes, foi de 89,3 dias.

CONCLUSÃO: Síndrome de nefrite e uveíte túbulo-intersticial já não é uma síndrome pediátrica, como se pensava. A apresentação parece ser variável, embora a nefrite túbulo-intersticial geralmente se apresente primeiro, associado a sintomas sistêmicos, como fadiga. À medida que os clínicos se tornam mais conscientes da doença, após a identificação do primeiro sintoma, os pacientes são acompanhados, porém, são necessários mais estudos para identificar o tempo de seguimento mais adequado. Relativamente ao tratamento, a maioria dos doentes respondeu aos corticosteroides, e apesar das recorrências, o prognóstico, foi no cômputo geral, favorável.

PALAVRAS-CHAVE: Nefrite Intersticial; Síndrome; Uveíte.

INTRODUCTION

Tubulointerstitial nephritis and uveitis (TINU) syndrome is a rare disease characterized by the occurrence of tubulointerstitial nephritis (TIN) and uveitis, in a patient with the absence of other systemic diseases that may be the cause of both or either; it is, therefore, a diagnosis of exclusion.[1,2] TIN is a potentially life-threatening condition, and typically, renal histology describe interstitial oedema with inflammatory cell infiltrates and tubular damage.[3]

It was first described in 1975 by Dobrin *et al*[4] and ever since, hundreds of cases have been reported, evincing a female predominance (2.5:1 to 5:1)[5,6] but also affecting more children and young adults.[6,7] TINU is thought to be a convergence of an immune mediated process with an environmental trigger,[7] such as drugs or infections, despite the fact that in many cases no cause is identified (idiopathic).[1] Considering that most uveitis cases have no identified cause it is important to consider TINU in the differential diagnosis, moreover the awareness of its possible associations with common systemic medications and infections. Given the heterogeneity that exists within both the uveitis spectrum and TIN, considering the anatomical subtype of uveitis and the heterogenous symptoms of TIN (there is also varied clinical presentations), the syndrome is likely to be underdiagnosed. Although the most common presentation is a bilateral sudden-onset anterior uveitis with typical symptoms of redness, pain and photophobia, ophthalmologists need to remain alert to the possibility of TINU in other clinical contexts.[8]

Whenever the occurrence of unexplained acute kidney injury (AKI) or progressive reduction in glomerular filtration rate (GFR) is present, TINU must be a differential diagnosis, since it accounts for about 15% of cases.[3]

The clinical presentation may vary from developing constitutional symptoms such as fever, rash, joint pain, malaise or flank tenderness to being asymptomatic (abnormal renal function detected with tests such as estimated GFR). Furthermore, the urine sediment also may differ, ranging from bland to active, with tubular proteinuria. However, albuminuria is not a very common finding.[8]

In most cases the diagnosis is presumed, lacking histological confirmation by means of renal biopsy. In order to confirm the diagnosis it is required a renal biopsy, exclusion of systemic diseases such as sarcoidosis, Sjogren's syndrome, systemic lupus erythematosus (SLE), and tubercu-

losis (TB).[9] Although standard treatment is not yet defined, it is consensual that topical and systemic corticosteroids are the option.[7-10] Prognosis is generally favorable, however progressive renal failure leading to renal transplant has been reported.[7]

Due to the diversity of clinical presentations, patient's heterogenous characteristics, lack of evidence regarding incidence and prevalence as well as the fact that most awareness of TINU derives form case report articles, we consider that a systematic review on the matter is required. Therefore, in face of the published articles available we aim to appraise and to clarify what is acknowledged in order to elucidate the demographics, risk factors, genetic predisposition, most frequent symptoms and laboratory findings, most adequate treatment and also TINU patient's prognosis. A systematic review is important in this context because it augments clinicians' awareness and offers them hints to what should be the next step in patient care.

METHODS

This systematic review of original literature was conducted in July 2021.

INCLUSION AND EXCLUSION CRITERIA

The study included scientific articles related with TINU syndrome. Inclusion criteria were planned taking into account evidence about patient, intervention, comparison and outcome (PICO) structure. In order to proceed with the investigation, we considered the following population: patients who presented with renal or ocular symptoms followed by a new episode of disease and weeks or months later being diagnosed with TINU syndrome. In the intervention we collected and compared this information from various scientific articles, combining them. The comparison was made with healthy subjects; therefore, they were not specified in the inclusion criteria.

The primary outcome was to provide a comprehensive clarification of the available evidence, in order to aid in future clinical-based decisions. The majority of papers are hospital-based since TINU syndrome is a diagnosis of exclusion. Therefore only after several diseases being ruled out, could the diagnosis be made. We did not exclude articles by publication data and the only ones that we excluded by language were the ones where the authors did not provide an English version after trying to contact them.

DATA SOURCE AND EXTRACTION

We searched the following databases: PubMed, Web of Science and Scopus.

Two authors independently screened all titles until eligibility was determined, taking into account exclusion and inclusion criteria, and extracted data from each eligible articles, which was summarized in a table to retrieve the following information: patients characteristics (age, sex and number), symptoms, diagnosis timing, laboratory and ophthalmological findings, treatment, relapse and follow up time, and reviewed independently by a third reviewer. Any doubtful situation was solved by consensus between the authors and there was a 100% agreement between authors in each step of study assessment.

The search used the following queries: ("tinu syndrome" or "uveitis and interstitial nephritis") and ("tinu" or "uveitis and tubulointerstitial nephritis"), according to PRISMA guidelines.

Quality assessment according to National Institute of Health criteria for observational cohort and cross-sectional studies (Table 1) and for case-series studies (Table 2) was performed. As well as critical appraisal checklist for case reports according to Joanna Briggs Institute (Table 3).

DATA ANALYSIS AND NARRATIVE SYNTHESIS

All relevant clinical studies were reviewed, and a table was made considering the type of article, mainly case reports, and were summarized considering epidemiology, symptoms, treatments, and prognosis (Table 4).

RESULTS

STUDY SELECTION

According to our research with the mentioned queries, 106 results were obtained from Scopus, 88 from Web of Science and 46 results from PubMed (Fig. 1). Resulting in 240 identified articles; 127 articles were duplicates, consequently excluded. 3 articles were written in foreign languages and did not provide an English version, therefore excluded; 9 articles were systematic reviews. In addition, 33 articles were not able to present full text available, being excluded. After screening, 4 articles did not respond to the objective clearly giving us 64 articles with full-text articles assessed for eligibility (Fig. 1).

A total of 64 articles were selected for the current study.

STUDY CHARACTERISTICS

Regarding the 64 articles, 5 were retrospective analyzes,[11-16] 6 were prospective studies,[16-21] 3 were case series,[22-24] and 50 were case reports[25-74] (Table 4), quality assessment analysis in Tables 1, 2 and 3, respectively.

Considering the lack of knowledge of this disease, all articles which filled in the criteria previously mentioned were included, therefore the sample size included articles that varied from 1 to 179 patients.

SYNTHESIS OF RESULTS

We found it impossible to calculate prevalence because the population targeted in this review only included confirmed cases of TINU.

The average age at diagnosis was 30.6 years-old, ranging from 4 to 66 years-old. Regarding gender predomi-

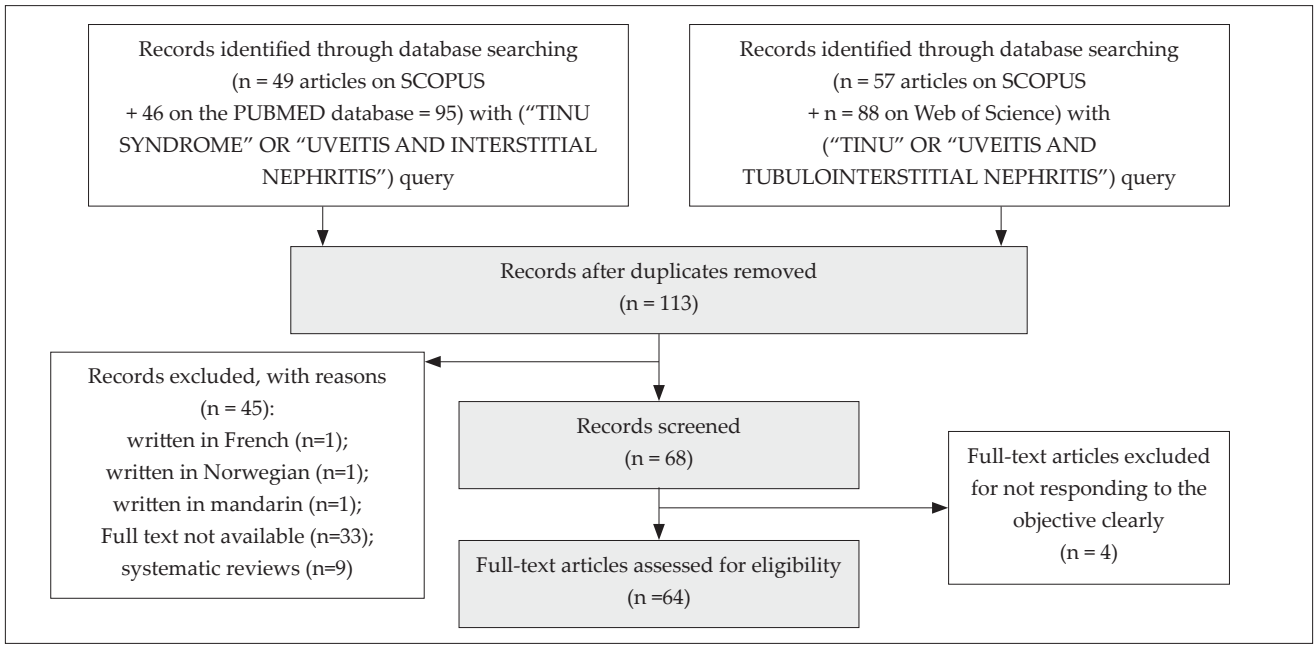

Figure 1. Flowchart showing literature search method with n representing the number of articles.

Table 1. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies according to Nacional Institute of Health criteria.

	LI *et al* (2014) [20]	TAN *et al* (2011) [21]	KANNO *et al* (2018) [14]	LEGENDRE *et al* (2016) [15]	HETTINGA *et al* (2015) [22]	HAYASHI *et al* (2020) [16]	ZHANG *et al* (2017) [17]	RYTKONEN *et al* (2018) [19]	JIA *et al* (2018) [23]	SU *et al* (2018) [24]	RYTKONEN *et al* (2021) [18]
Was the research question or objective in this paper clearly stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the study population clearly specified and defined?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the participation rate of eligible persons at least 50%?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was a sample size justification, power description, or variance and effect estimates provided?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y
Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Y	NA	NA	Y	Y	Y	NR	NR	NR	Y	Y
For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	NA	NA	NA	NA	Y	Y	NR	NA	NA	NA	NA
Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the exposure(s) assessed more than once over time?	Y	NA	NA	NA	Y	NR	NR	NA	NA	NA	NR
Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were the outcome assessors blinded to the exposure status of participants?	NR	NA	NA	NA	NR	NR	NR	NA	NA	NR	NR
Was loss to follow-up after baseline 20% or less?	Y	Y	NA	NR	Y	NR	NR	NA	NR	NR	NR
Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Y	NR	NR	Y	Y	NR	NR	NR	NR	NA	NA
Quality rating	GOOD	GOOD	FAIR	GOOD	GOOD	GOOD	FAIR	FAIR	FAIR	GOOD	GOOD

Y - Yes; NR - Not Reported; NA – Not Applicable

Table 2. Quality Assessment Tool for Case-Series Studies according to National Institute of Health criteria.

	ROY *et al* (2017) [11]	CHOI *et al* (2019) [12]	PROVENCHER *et al* (2018) [13]
Was the study question or objective clearly stated?	Y	Y	Y
Was the study population clearly and fully described, including a case definition?	Y	Y	Y
Were the cases consecutive?	Y	Y	Y
Were the subjects comparable?	Y	Y	Y
Was the intervention clearly described?	Y	Y	Y
Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y
Was the length of follow-up adequate?	Y	NR	Y
Were the statistical methods well-described?	NA	NA	NA
Were the results well-described?	Y	Y	Y
Quality Assessment	GOOD	FAIR	GOOD

Y - Yes; NR - Not reported; NA - Not applicable

Table 3.(1) Critical Appraisal Checklist for case reports according to Joanna Briggs Institute.

	SALU *et al* (1990) [25]	ERDOGMUS *et al* (2016) [26]	PINHEIRO *et al* (2016) [27]	HABIB *et al* (2003) [28]	SHIMAMURA *et al* (2014) [29]	DERBEL *et al* 2020 [30]	FRAGA *et al* (2014) [31]	NAGASHIMA *et al* (2015) [32]	BARUT *et al* (2015) [33]	PURT *et al* (2016) [41]	MENEZO *et al* (2004) [42]	ISNARDI *et al* (2016) [43]	PEREIRA *et al* (2016) [44]
Were patient's demographic characteristics clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the patient's history clearly described and presented as a timeline?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the current clinical condition of the patient on presentation clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were diagnostic tests or assessment methods and the results clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the intervention(s) or treatment procedure(s) clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the post-intervention clinical condition clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were adverse events (harms) or unanticipated events identified and described?	NR	Y	Y	Y	NR	Y	Y	Y	Y	NR	NR	NR	NR
Does the case report provide takeaway lessons?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Overall appraisal	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE

Y - Yes; NR - Not Reported; NA – Not Applicable

Table 3.(2) Critical Appraisal Checklist for case reports according to Joanna Briggs Institute.

	CARVALHO *et al* (2018) [45]	NISHI *et al* (2020) [45]	VÔ *et al* (2018) [34]	AOYAGI *et al* (2014) [35]	SUGIYAMA *et al* (2018) [36]	NAVARRO *et al* (1997) [37]	ZHAO *et al* (2020) [38]	KAMEL *et al* (2014) [39]	MATSUMOTO *et al* (2015) [40]	KASHIWAGI *et al* (2009) [47]	KAWAMATA *et al* (2016) [48]	PALADINI *et al* (2013) [49]	ZHOU *et al* (2012) [50]
Were patient's demographic characteristics clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the patient's history clearly described and presented as a timeline?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the current clinical condition of the patient on presentation clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were diagnostic tests or assessment methods and the results clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the intervention(s) or treatment procedure(s) clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the post-intervention clinical condition clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were adverse events (harms) or unanticipated events identified and described?	Y	NR	Y	NR	Y	NR	Y	Y	Y	NR	Y	NR	Y
Does the case report provide takeaway lessons?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Overall appraisal	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE

Y - Yes; NR - Not Reported; NA – Not Applicable

Table 3.(3) Critical Appraisal Checklist for case reports according to Joanna Briggs Institute.

	ABED *et al* (2007) [51]	ONYEKPE *et al* (2011) [52]	PATNAIK *et al* (2020) [53]	LEI *et al* (2015) [54]	THOMASSEN *et al* (2009) [55]	SINANGIL *et al* (2016) [56]	HAN *et al* (2012) [57]	KIM *et al* (2016) [58]	GORRONO-ECHEBARRÍA *et al* (2001) [59]	TEKIN *et al* (2020) [60]	AGARWAL *et al* (2020) [61]	ZONNEVYLLE *et al* (2019) [62]
Were patient's demographic characteristics clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the patient's history clearly described and presented as a timeline?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the current clinical condition of the patient on presentation clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were diagnostic tests or assessment methods and the results clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the intervention(s) or treatment procedure(s) clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the post-intervention clinical condition clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were adverse events (harms) or unanticipated events identified and described?	NR	Y	Y	NR	Y	Y	NR	Y	NR	NR	NR	NR
Does the case report provide takeaway lessons?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Overall appraisal	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE

Y - Yes; NR - Not Reported; NA – Not Applicable

Table 3.(4) Critical Appraisal Checklist for case reports according to Joanna Briggs Institute.

	STEWART *et al* (2020) [63]	MORTAJIL *et al* (2006) [64]	TAHERI *et al* (2009) [65]	ARIBA *et al* (2017) [66]	SINNAMONA *et al* (2008) [67]	BROGAN *et al* (2012) [67]	ROMÁN *et al* (2004)69	SKALOVA *et al* (2017) [70]	SEKIGUCHI *et al* (2007) [71]	PEPPLE *et al* (2015) [72]	HEYMANN *et al* (2015) [73]	LAVA *et al* (2011) [74]
Were patient's demographic characteristics clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the patient's history clearly described and presented as a timeline?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the current clinical condition of the patient on presentation clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were diagnostic tests or assessment methods and the results clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the intervention(s) or treatment procedure(s) clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the post-intervention clinical condition clearly described?	Y	Y	Y	Y	Y	Y	Y	y	Y	Y	Y	Y
Were adverse events (harms) or unanticipated events identified and described?	NR	NR	NR	NR	Y	NR	NR	NY	Y	Y	Y	NR
Does the case report provide takeaway lessons?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Overall appraisal	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE	INCLUDE

Y - Yes; UN - Unclear; NA - Not Applicable

nance our calculated ratio was 2:1, (female: male, respectively). Moreover, TINU syndrome does not appear to be associated with race or ethnicity.

Concerning TINU presentation symptoms, as it is known TINU diagnosis implies the manifestation of both of TIN and uveitis, but not always simultaneously; therefore, the diagnosis can only be made when the second manifestation appears. In fact, we observed that TIN preceded uveitis in 50.4% of cases, the reverse in 33.3% and occur simultaneously in 16.2%. The mean time between the symptoms was 73.7 days, ranging from 0 to 730 days.

Amongst uveitis cases 90.0% were anterior uveitis, 4.88% were intermediate uveitis and 0.3% were panuveitis - the remaining were not specified; moreover 12.7% of uveitis cases were granulomatous. Considering laterality, 82.5% were bilateral and 11.1% were unilateral - the remaining were not specified.

Furthermore, the most common systemic symptoms were fatigue (33.2%), fever (28.3%), weight loss (28.2%), anorexia (17.3%), nausea (14.0%), vomiting (13.1%) and abdominal pain (12.5%). Less frequently: headaches (11.7%), myalgias and arthralgias (10.3%), polyuria (8.5%), malaise (8.0%), respiratory symptoms as cough and dyspnea (7.0%), nocturia (4.2%), polydipsia (4.2%) and diarrhea (1.4%).

The majority of patients who presented either with uveitis or TIN, were submitted to both blood and urine analysis. The most common findings in blood analysis were elevated serum creatinine (73.8%), elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels (54.0%), elevated blood urea nitrogen level (BUN) (39.4%), anemia (29.5%), decrease in estimated glomerular filtration rate (eGFR) (23.6%), leukocytosis (11.3%), elevated aspartate transaminase/alanine aminotransferase (respectively AST/ALT) (2.8%), serum β2-microglobulin (β2-MG) (2.8%), elevated uric acid (1.4%) and also lactic acid dehydrogenase (LDH) (1.4%). The immunologic markers showed that some patients were found to have elevated Immunoglobulin G levels (9.9%), positive antinuclear antibodies (ANA) (8.7%), Immunoglobulin A levels (5.6%), positive KL-6 (1.6%), elevated angiotensin-converting enzyme (ACE) (1.4%), cystatine C (1.4%) and MB isoenzyme creatine kinase (1.4%). Urinalysis showed proteinuria (64.0%), glycosuria (45.1%), elevated urinary β2-MG (42.8%), hematuria (24.5%), elevated urinary N-acetyl-beta-glucosamynidase (NAG) excretion (14.4%), elevated protein/creatinine ratio (12.7%), elevated microglobulin-α1 (9.9%), leukocyturia (9.8%), albumin/creatinine ratio (4.2%) and hemoglobinuria (1.4%).

Most patients were submitted to a renal biopsy not only to make the diagnosis but also to exclude some other potential diagnosis. The majority presented diffuse interstitial inflammation/nephritis (91.4%), tubulitis (43.2%), interstitial fibrosis (26.7%), mesangial hypercellularity (7.1%). Moreover 14.7% of patients had granulomatous nephritis. In immunofluorescence, immunoglobulin and complement deposits were observed, C3 deposits on endothelium (5.5%), IgA (5.5%), IgG (5.4%) and IgM (1.9%).

Ocular evaluation was also a very important step in patients' care; however, in a large number of patients only uveitis was reported. Of those submitted to ocular evaluations, 52.0% reported keratic precipitates on anterior chamber (of which 12.7% were granulomatous). 20.8% had papilledema, 10.4% posterior synechiae, 8.8% vitreous opacities, 6.8% retinal exudates, 6.0% had snowballs, 2% had retinal hemorrhages. Although the remaining 32.0% did had an ocular evaluation, only "uveitis" was reported.

Regarding treatment, we observed that 78.8% of patients were putted on oral corticosteroids, of which 21.9% required an additional immunosuppressor. The most used immunosuppressors were: mycophenolate mofetil (29.8%), azathioprine (28.0%), cyclophosphamide (24.6%) and methotrexate (16.4%).

Table 4.(1) Article selection, with study type, number of patients, symptoms, diagnosis, treatment, relapse and follow up time.

SOURCE	STUDY TYPE	PATIENTS (N)	PRESENTATION SYMPTOMS	UVEITIS	TIME BETWEEN THEM (DAYS)	DIAGNOSIS AND TREATMENT	RELAPSE (MEAN TIME IN DAYS)	FOLLOW-UP (MONTHS)
LI *et al* (2014) [20]	Prospective study	31	Fatigue, anorexia, nausea, vomiting, fever, polyuria and nocturia	Anterior uveitis (58% bilateral)	42% uveitis occurred concurrently or before TIN. 58% developed late-uveitis (60-425 days later)	100% Prednisone 36% Cyclophosphamide	180	12
SALU *et al* (1990) [25]	Case report	1	Fatigue anorexia	Unilateral anterior uveitis.	180	Oral methylpredisone. Topical treatment (neomycin sulphate, polymyxin B, dexamethasone drops and with atropine 1%)	Without relapse during follow-up time	>6
ERDOGMUS *et al* (2016) [26]	Case report	1	Fatigue, malaise, anorexia and headache	Bilateral anterior uveitis.	120	Systemic prednisone. Topical corticosteroids	Without relapse during follow-up time	6
TAN *et al* (2011) [21]	Prospective study	9	Fever, fatigue weight loss and lymph node enlargement	NR	150	100%-topical steroid 89% - Oral prednisone 22% - cyclophosphamide	Without relapse during follow-up time	>12
PINHEIRO *et al* (2016) [27]	Case report	1	Bilateral eye pain and redness	Bilateral anterior uveitis.	90	Topical steroids; Prednisolone; Corticosteroids, eye drops and ketorolac; Cyclosporine ophthalmic emulsion.	90	52
HABIB *et al* (2003) [28]	Case report	1	Myalgias	Intermediate bilateral uveitis.	30	Topical and subtenon corticosteroids.	90	NR
SHIMAMURA *et al* (2014) [29]	Case report	1	Sore throat, hematuria, fever, chills, and fatigue	Bilateral anterior uveitis.	365	Oral prednisolone	Without relapse during follow-up time	NR
DERBEL *et al* (2020) [30]	Case report	1	Anterior uveitis of the right eye	Granulomatous anterior unilateral uveitis	NR	Prednisone. Ocular corticosteroid and mydriatic eye drops.	730	72
FRAGA *et al* (2014) [31]	Case report	1	Asthenia, anorexia, weight loss and oliguria	Bilateral anterior uveitis.	90	Oral prednisolone Topical steroid	120	24
NAGASHIMA *et al* (2017) [32]	Case report	1	Left eye pain, reduced visual acuity and flu-like symptoms	Bilateral anterior uveitis.	10	Oral prednisolone	60	NR
NAGASHIMA *et al* (2017) [32]	Case report	1	Right eye pain	Bilateral anterior uveitis.	90	Triamcinolone acetonide injection in the sub-Tenon's capsule	Without relapse during follow-up time	NR
NAGASHIMA *et al* (2017) [32]	Case report	1	Laboratorial findings of decreased renal function	Granulomatous anterior bilateral uveitis	365	Oral prednisolone; Ocular steroid	90	NR
BARUT *et al* (2015) [33]	Case report	1	extreme fatigue, loss of appetite and weight loss.	Granulomatous anterior bilateral uveitis	10	Prednisone	Without relapse during follow-up time	20
VÖ *et al* (2018) [34]	Case report	1	bilateral painful red eyes and photophobia	Bilateral anterior uveitis	30	Methylprednisolone; Topical corticosteroid therapy with a cycloplegic agent	Without relapse during follow-up time	NR
AOYAGI *et al* (2014) [35]	Case report	1	Mild proteinuria and weight loss	Unilateral anterior uveitis.	120	Topical steroids; Anticholinergic.	Without relapse during follow-up time	48
SUGIYAMA (2018) [36]	Case report	1	Fever, respiratory symptoms, and malaise	Bilateral anterior uveitis.	14	Oral prednisolone	Without relapse during follow-up time	NR
NAVARRO *et al* (1997) [37]	Case report	1	cough, malaise, weakness and headache	Bilateral anterior uveitis.	5	Topical dexamethasone and atropine 1%; Oral prednisone treatment	21	6
ZHAO *et al* (2020) [38]	Case report	1	Nausea, fatigue and blurred vision.	Fundoscopy examination revealed fundal hemorrhage	120	Telmisartan and oral prednisolone ral cyclophosphamide.	180	NR
KAMEL *et al* (2014) [39]	Case report	1	Polyuria, polydipsia, and generalized weakness	Bilateral anterior uveitis.	7	Oral prednisone	Without relapse during follow-up time	9
MATSUMOTO *et al* (2015) [40]	Case report	1	Low grade fever, weight loss, fatigue, anorexia and arthralgias	Bilateral anterior uveitis.	60	Topical corticosteroids; Oral prednisolone	Without relapse during follow-up time	12
PURT*et al* (2016)41	Case report	1	Nausea, vomiting, and abdominal pain and bilateral eye redness	Bilateral anterior uveitis.	0	Oral prednisone; Prednisolone acetate ophthalmic.	Without relapse during follow-up time	6
KANNO *et al* (2018) [14]	Retrospective study	5	Eye redness in 100%, eye pain 80%, and a decrease in vision in 60%. Both eyes were affected in 100%.	Bilateral anterior uveitis.	7	Topical corticosteroids and systemic steroids.	885	54
MENEZO *Et al.* (2004) [42]	Case report	1	Painless, hazy vision in both eyes	Bilateral anterior uveitis.	0	Topical dexamethasone 0.1%; Oral Prednisolone.	180	18
ISNARDI *et al* (2016) [43]	Case report	1	Nausea, vomiting and diarrhea	Bilateral anterior uveitis.	7	Oral prednisolone; Topical corticosteroids	Without relapse during follow-up time	NR
PEREIRA *et al* (2018) [44]	Case report	1	Blurred vision, redness, pain in the right eye and weight loss.	Bilateral anterior uveitis.	0	Ocular dexamethasone, mydriatics; Oral prednisolone.	60, 365 and 1095	60
CARVALHO *et al* (2019) [45]	Case report	1	Fever, chills, headache, malaise and myalgia	Bilateral anterior uveitis.	2	Topical prednisolone	Without relapse during follow-up time	18

NR – not reported.

Table 4.(2) Article selection, with study type, number of patients, symptoms, diagnosis, treatment, relapse and follow up time.

SOURCE	STUDY TYPE	PATIENTS (N)	PRESENTATION SYMPTOMS	UVEITIS	TIME BETWEEN THEM (DAYS)	DIAGNOSIS AND TREATMENT	RELAPSE (MEAN TIME IN DAYS)	FOLLOW-UP (MONTHS)
NISHI *et al* (2020) [46]	Case report	1	Blurred vision and declined visual acuity	Granulomatous anterior bilateral uveitis	7	Oral prednisolone; Antivascular endothelial growth factor.	90, 120	24
KASHIWAGI *et al* (2009) [47]	Case report	1	Ocular pain, redness and photophobia	Bilateral anterior uveitis.	150	Predonisolone eye drops; Predonisolone	60	NR
KAWAMATA *et al* (2016) [48]	Case report	1	Spiked fever and a loss of appetite.	Bilateral anterior uveitis.	17	Oral prednisolone; Topical corticosteroids	Without relapse during follow-up time	NR
LEGENDRE *et al* (2016) [15]	Retrospective study	41	Renal symptoms preceded the uveitis in 20%, uveitis preceded the renal symptoms in 31% and 49%, the eye and kidney symptoms were concomitant.	NR	60-90	85% oral corticosteroids and cortisone eye drops.	40% in the first 365 days	17.8
PALADINI *et al* (2013) [49]	Case report	1	Fever, shivering, fatigue and loss of appetite.	Bilateral anterior uveitis.	0	Oral prednisone	Without relapse during follow-up time	5
HETTINGA *et al* (2015) [22]	Prospective cohort study	45	uveitis31% had intermediate uveitis and 2% had panuveitis.	49% - intermediate uveitis29% anterior uveitis20%-panuveitis1%-posterior uveitis84% - bilateral uveitis16% - unilateral uveitis	240	NR	Without relapse during follow-up time	60
ZHOU *et al* (2012) [50]	Case report	1	Fatigue, low-grade fever, increased nocturia, and weight loss	Right anterior uveitis	5	Oral prednisone; prednisone eye drops	Without relapse during follow-up time	60
ABED *et al* (2008) [51]	Case report	1	Light sensibility, red eyes and ocular pain.	Bilateral anterior uveitis.	90	Prednisone; Mycophenolate mofetil associated with low-dose prednisolone.	60	NR
ONYEKPE *et al* (2011) [52]	Case report	1	Weight loss, pallor, poor appetite, nausea and intermittent abdominal pain.	Bilateral anterior uveitis.	150	Oral prednisolone; Topical eye treatment.	1095 At 17 years of age, received a pre-dialysis renal transplant with TINU recurrence after 3.5 years, transplant biopsy revealed granulomatous interstitial nephritis.	NR
HAYASHI *et al* (2021) [16]	Retrospective observational study	29	24% showed general symptoms and 75% showed ocular symptoms.	NR	General symptoms preceded the ocular symptoms: median 1.4 months;Ocular symptoms preceded the general symptoms: median 3.2 months.	100% received treatment with topical/oral corticosteroids or oral methotrexate.	NR	38
PATNAIK *et al* (2020) [53]	Case report	1	Redness, pain, blurring of vision in both eyes and recurrent febrile illness.	Bilateral anterior uveitis.	150	Oral prednisolone; Oral mycophenolate mofetil;Topical nonsteroidal anti-inflammatory eye drops.	Without relapse during follow-up time	>1
LEI *et al* (2015) [54]	Case report	1	Fever, extreme fatigue, loss of appetite, and shivering.	Bilateral anterior uveitis.	30	Oral prednisone	Without relapse during follow-up time	6
THOMASSEN *et al* (2009) [55]	Case report	1	Sore throat, general fatigue, weight loss, asthenia, anorexia and recurrent abdominal pain.	Bilateral anterior uveitis.	7	Oral prednisone	Without relapse during follow-up time	18
SINANGIL *et al* (2016) [56]	Case report	1	Burning pain and hazy vision in both eyes.	Bilateral anterior uveitis.	21	Oral prednisolone; Topical corticosteroid.	Without relapse during follow-up time	NR
HAN *et al* (2012) [57]	Case report	1	Anterior uveitis	Bilateral anterior uveitis.	7	Oral prednisolone; Topical steroid.	Without relapse during follow-up time	NR
KIM *et al* (2016) [58]	Case report	1	Anterior bilateral uveitis	Bilateral anterior uveitis.	30	Oral prednisolone, deflazacort and azathioprine.	Without relapse during follow-up time	>68
GORROÑO-ECHEBARRÍA *et al* (2001) [59]	Case report	1	Nausea and anorexia	Bilateral anterior uveitis.	120	Expectant	Without relapse during follow-up time	NR
GORROÑO-ECHEBARRÍA *et al* (2001) [59]		1	Upper respiratory infection	Bilateral anterior uveitis.	NR	Expectant	Without relapse during follow-up time	NR
GORROÑO-ECHEBARRÍA *et al* (2001) [59]		1	Asymptomatic, coincidental finding	Bilateral anterior uveitis.	150	Expectant	Without relapse during follow-up time	NR
TEKIN *et al* (2020) [60]	Case report	1	Extreme fatigue, anorexia and weight loss	Granulomatous anterior bilateral uveitis	14	Topical 1% prednisolone acetate and 1% cyclopentolate; Oral corticosteroids	Without relapse during follow-up time	24
AGARWAL *et al* (2020) [61]	Case report	1	Redness and pain in the right eye (RE) along with low-grade fever and headache.	Bilateral anterior uveitis.	0	Topical prednisolone eye drops 1% QID and cycloplegics BD; Oral steroids	Without relapse during follow-up time	9

NR – not reported.

Table 4.(3) Article selection, with study type, number of patients, symptoms, diagnosis, treatment, relapse and follow up time.

SOURCE	STUDY TYPE	PATIENTS (N)	PRESENTATION SYMPTOMS	UVEITIS	TIME BETWEEN THEM (DAYS)	DIAGNOSIS AND TREATMENT	RELAPSE (MEAN TIME IN DAYS)	FOLLOW-UP (MONTHS)
AGARWAL *et al* (2020) [61]	Case report	1	Acute interstitial nephritis	Bilateral anterior uveitis.	90	Oral steroid;Topical prednisolone acetate 1% eye drops QID and cyclopegics BD; Methotrexate	Without relapse during follow-up time	17
AGARWAL *et al* (2020) [61]	Case report	1	Chronic renal failure and chronic uveitis.	Bilateral anterior uveitis.	NR	Steroid cover.	Without relapse during follow-up time	12
ZONNEVYLLE *et al* (2019) [62]	Case report	1	General weakness, and high fever.	Bilateral anterior uveitis.	180	Systemic methylprednisolone; Topical steroids.	365	NR
STEWART *et al* (2020) [63,81]	Case report	1	Anorexia, weight loss, flu-like symptoms and dryness of his eyes.	Bilateral anterior uveitis.	NR	Paracetamol.	Without relapse during follow-up time	NR
MORTAJIL *et al* (2006) [64]	Case report	1	Bilious vomiting, diffuse arthralgia and loss of weight.	Bilateral anterior granulomatous uveitis.	90	Oral prednisolone; Local mydriatics and corticosteroids.	90	24
MORTAJIL *et al* (2006) [64]	Case report	1	Post prandial vomiting with epigastric discomfort, right rib pain and loss of weight.	Bilateral anterior granulomatous uveitis.	60	Oral prednisolone; Local steroid therapy.	30	27
ARIBA *et al* (2017) [66]	Case report	4	Fever, weight loss, anorexia, abdominal and flank pain; Redness of the eye and blurred vision, anterior uveitis and episcleritis.	Unilateral anterior uveitis.	Nephritis preceded uveitis in 25%. Nephritis followed ocular manifestations in 75%.	Topical corticosteroid treatment; Oral corticosteroid.	25% after 180	NR
SINNAMON *et al* (2008) [67]	Case report	1	Bilateral anterior uveitis.	Bilateral anterior uveitis	42	Oral prednisolone; Topical treatment;Methylprednisolone.	14	24
BROGAN *et al* (2012) [68]	Case report	1	Bilateral acute anterior uveitis.	Bilateral anterior uveitis	30	Oral prednisolone; corticosteroids eye drops; Azathioprine;Mycophenolate mophetil.	Without relapse during follow-up time	NR
SU *et al* (2018) [24]	Prospective study	157	Weakness (57.3%), nausea and vomiting (65.0%) and loss of weight (67.5%).	Bilateral anterior uveitis	60	Oral prednisone-91.1%; 42.7% - mycophenolate, azathioprine and cyclophosphamide.	Recurrent kidney injury was observed in 26.1% in the first 30 days	NR
ZAMORA *et al* (2004) [69]	Case report	1	Intermediate chronic uveitis (pars plans) and bilateral ocular pain	Intermedia uveitis	730	Expectant	NR	NR
SKALOVA *et al* (2017) [70]	Case report	1	Anterior uveitis	Unilateral anterior uveitis	Uveitis before nephritis.	Oral prednisolone	60	NR
ZHANG *et al* (2017) [17]	Retrospective study	24	NR	NR	NR	NR	NR	NR
SEKIGUCHI *et al* (2007) [71]	Case report	1	Fever and general fatigue	NR	60	Oral prednisolone	Without relapse during follow-up time	NR
ROY *et al* (2020) [11]	Case Series	10	Polydipsia, nausea, vomiting, abdominal pain, reduced appetite, malaise, lethargy, joint pains, rash, eye pain and headaches.	NR	Eye symptoms was prior to AIN presentation in 33%, simultaneous in 33% and after AIN presentation in 33%.	80% - oral prednisolone	Without relapse during follow-up time	18.5
PEPPLE *et al* (2015) [72]	Case Report	1	Right eye redness, pain, photophobia, and blurry vision.	Bilateral anterior uveitis	120	Prednisolone acetate 1% drops, difluprednate drops, and homatropine and timolol/brimonidine combination drops. Oral prednisone.	Without relapse during follow-up time	NR
HEYMANN *et al* (2015) [73]	Case report	1	Inflamed, painful left eye with decreased vision in the left eye. Laboratory findings of decreased renal function.	Unilateral anterior uveitis	0	Intravitreal injections of ranibizumab.	365	NR
CHOI *et al* (2019) [12]	Case Series	179 – 6 with TINU (11.5%)	Idiopathic uveitis: 83.3% had anterior uveitis and 16.7% had intermediate uveitis. Bilateral 100%	NR	NR	NR	Without relapse during follow-up time	NR
PROVENCHER *et al* (2018) [13]	Case Series	9	All patients had ocular symptoms and 33% had systemic symptoms.	All patients had bilateral uveitis, and 67% had primarily anterior uveitis.		100% topical steroids;89% oral steroids; 22% mycophenolate mofetil.	22% of patients recurred, within the 365 days.	36.2
LAVA *et al* (2011) [74]	Case report	1	Fever and headache.	Anterior bilateral uveitis.	60	methylprednisolone endovenous 10 mg/kg for 3 days, followed by oral prednisolone 80 mg daily for 4 months and topical corticosteroids	60	NR
JIA *et al* (2018) [23]	Prospective study	154	1000% presented with ATIN.	NR	NR	NR	NR	12
RYTKÖNEN *et al* (2021) [18]	Retrospective study	52	Fever, fatigue, and weight loss.	In 12% uveitis appeared 3-10 months after TIN. In most cases, uveitis was diagnosed at the same time	30-300	87% oral prednisolone and topical prednisone; 4% methotrexate; 2% mycophenolate mofetil;2% adalimumab.	Without relapse during follow-up time	5.7
RYTKÖNEN *et al* (2018) [19]	Prospective study	33	NR	NR	NR	NR	Without relapse during follow-up time	12

NR – not reported.

RELAPSE

Despite corticotherapy, 48.3% of patients still relapsed, the majority after stopping the treatment with corticosteroids (70.4%). However, 14.8% were considered steroids dependent, relapsed while tapering the treatment, when therapeutic doses where no longer administered; 11.1% were steroid-resistant's', meaning relapse during therapeutic doses of corticosteroids. Moreover, 3.7% relapsed after treatment with methotrexate. The mean time between the diagnosis and the relapse was 89.3 days, ranging from 14 days to 1295 days (Table 5).

Relapse presented most frequently as anterior uveitis (57.7%), but 26.9% revealed as interstitial nephritis, with 7.7% of patients with both simultaneously. There was also, 3.8% of patients with intermedia uveitis and others 3.8% with sudden decreased vision.

The approach taken by clinicians regarding relapse was somehow variable, ranging from topical corticosteroids alone, to the combination of both topical corticosteroids and oral immunosuppressors (corticosteroids, methotrexate, mycophenolate mofetil and azathioprine). However, others preferred a systemic approach with either, high dose of corticosteroids, low dose of corticosteroids together with a second immunosuppressor or purely a non-steroid immunosuppressor such as methotrexate, mycophenolate mofetil, azathioprine and cyclophosphamide. There was also a small percentage of patients who received intravitreal injections of biological therapy (ranibizumab).

DISCUSSION

PREVALENCE

TINU diagnosis seems to be underrecognized since some of the affected patients often fail to seek medical care, which probably underestimates the prevalence of the disease. The non-specificity of the initial symptoms may be the cause, since both nephritis and uveitis may present with mild and indolent symptoms, delaying the etiological investigation.[1,2] Moreover, the fact that TIN diagnosis is histological and requires a renal biopsy, which entails several risks that many patients and clinicians are not willing to take, causes the diagnosis to be simply presumptive.

Therefore, the prevalence, is expected to be higher than reported. The possible prevalence of TINU ranges wildly from 0.1% to 2.3%, depending on the population involved. Mackenses et al during a 20 year period of survey, reported

Table 5. Correlation between age, sex and relapse timing.

	AGE (YEARS)	SEX	RELAPSE	RELAPSE TIME (DAYS)
LI *et al* [20]	47.7+- 12.1;	Female predominance (5.2:1)	TIN	180d – while tapering CS therapy
PINHEIRO *et al* [27]	60	Female	Anterior uveitis	90d - after CS therapy
HABIB *et al* [28]	56	female	Intermedia uveitis	90d - after CS therapy
DERBEL *et al* [30]	47	Female	Anterior uveitis	730d - after CS therapy
FRAGA *et al* [31]	55	Female	Anterior uveitis	150d - after CS therapy
NAGASHIMA *et al* [32]	15	Male	Anterior uveitis	60d - after CS therapy
NAGASHIMA *et al* [32]	49	Female	Anterior uveitis	90d - after CS therapy
NAVARRO *et al* [37]	15	Male	Anterior uveitis	21d - after CS therapy
ZHAO *et al* [38]	37	Male	TIN	180d - after CS therapy
KANN *et al* [14]	15.8	Female predominance (1.5:1)	NR	885d - after CS therapy
MENEZO *et al* [44]	24	Female	NR	180d - after CS therapy
PEREIRA *et al* [44]	13	Female	Anterior uveitis	60d – after MTX therapy
NISHI *et al* [46]	13	Female	Anterior uveitis	90d - after CS therapy
KASHIWAG *et al* [47]	12	Female	Anterior uveitis	60d - while tapering CS therapy
LEGENDRE *et al* [15]	46.8	Female predominance (1.6:1)	Anterior uveitis	40% in the first 365d after CS therapy
ABED *et al* [51]	15	Male	Anterior uveitis	60d - while tapering CS therapy
ONYEKPE *et al* [52]	8	Male	TIN	1095d - after CS therapy
ZONNEVYLLE *et al* [62]	67	Female	TIN	365d - after CS therapy
MORTAJIL *et al* [64]	35	Female	Anterior uveitis	90d - during CS therapy
MORTAJIL *et al* [64]	40	Female	Anterior uveitis	30d - during CS therapy
ARIBA *et al* [66]	54.8 ± 12.3	50% female, 50% male (1:1)	TIN	25% in the first 180d after CS therapy
SINNAMON *et al* [67]	39	Male	Anterior uveitis	14d - after CS therapy
SU *et al* [24]	47.2	Female predominance (1.3:1)	TIN	26.1% in the first 30d after CS therapy
SKALOVA *et al* [70]	14	Male	Anterior uveitis and TIN	60d - while tapering CS therapy
HEYMANN *et al* [73]	34	Female	Sudden decreased vision	365d - after CS therapy
PROVENCHER *et al* [13]	33.4	Female predominance (1.12:1)	Anterior uveitis	32.2% in the first 65d - after CS therapy
LAVA *et al* [74]	14	Female	Anterior uveitis	60d - during CS therapy

CS – corticosteroids; MTX – methotrexate; TIN – tubulointerstitial nephritis

a prevalence of 1.7%.[3] On the other hand, most series, report prevalence between 0.2%–0.6%.[4-9]

AGE

We observed that the average age in TINU syndrome diagnosis was 30.6 years-old, ranging from 4 to 66 years-old. Therefore, it seems that it is not simply a pediatric syndrome as many have pointed out. In fact, since clinicians, not only pediatric, have become more aware, the diagnosis has been increasing and the association of uveitis and TIN does not go unnoticed, affecting among others, older patients, rising the medium age of diagnosis. As observed by Giralt *et al*,[75] 18.8% of their population were diagnosed in their sixties.

SEX

Unlike Mackensen *et al* (2007), that found a male:female ratio of 3:2,[3] there seems to be a consensus, within our article series, of a female predominance of TINU syndrome with an estimated ratio of 2:1, female:male (respectively). The reason for this predominance is yet to be discovered, some authors supposing that females are more susceptible to autoimmune disease while others point to a genetic cause.[52] However, since the true cause of TINU syndrome is not yet established, the true reason of female predominance remains unknown.

ETHNICITY

As observed by Mandeville *et al*[9] we also did not found any race or ethnicity association.

Choi *et al*[23] analyzed patients' ethnicity, the majority being Caucasian (75.4%), Hispanic (8.4%), Asian (3.9%), African American (3.4%) and others (3.4%), however no conclusion could be made, seen that the study population was conducted in a country were Caucasian predominate in the population.

A couple of studies suggest a higher prevalence of TINU in northern European populations,[22,76] even though it remains unclear if greater awareness of TINU as a disease entity may be contributing to higher screening and diagnosis rates.

GENETIC

Genetic factors have been an area that many authors have focused on. Although numerous associations were researched, Human Leukocyte Antigen (HLA) typing is the predominant.

Jia *et al*[20] concluded that patients with HLA-DQA1, -DQB1, and -DRB1 alleles have genetic susceptibility for TINU syndrome. Moreover, the HLA-DQA1*0104/DQB1*0503/DRB1*1405 contribute to an increasing risk for development of TINU, facilitating renal tubulointerstitial inflammation by augmenting Ag-presenting capacity of renal tubular cells.

According to Kanno *et al*,[11] HLA typing may help in the diagnosis of TINU as they have perceived that HLA-DR4 or the allele of DRB1 *04 was present in all (100%) patients.

Reddy *et al* identified and associated HLA- DR and –DQ alleles with TINU and considered them "risk alleles".[10]

Matsumoto *et al*[40] obtained data on the HLA results from 50 healthy Japanese subjects and found no significant differences in the specific HLA types between those with and without the disease.

Mackensen *et al*[3] and Mandeville *et al*[9] reported a higher frequency of HLA-DR1 amongst patients with TINU syndrome. However, Giralt *et al*[75] found that HLA-DQB1*05 was higher amongst Iberian population, with TINU syndrome, suggesting a genetically specific feature of Spanish and Portuguese patients; moreover, they found a possible association between having HLA-DQB1*05 and the presence of posterior synechiae and poorer renal function.

Rytkonen *et al* concluded that genetic variation in the inflammatory mediators may predispose to autoimmune nephritis and uveitis, in the population who has *IL-10+434T* and *+504G* alleles and the genotype -2849TT are more likely to develop TINU syndrome than control population. This HLA association favors autoimmune hypothesis, as it is known its association with autoimmune diseases, such as rheumatoid arthritis.[15]

RISK FACTORS

Risk factors, such as previous infections and medications were studied by various authors, however no clear association could be made to any possible risk factor.

A systemic disease process similar to TINU but secondary to hantavirus infection was reported by Stewart et al63 Hantavirus is transmitted by rodents; when facing a patient with idiopathic acute kidney injury, clinicians should be aware and question possible exposures to those animals.

Nevertheless, when a patient presents with uveitis or acute kidney injury, the follow-up surveillance should be very narrow.

DIFFERENTIAL DIAGNOSIS

Since TINU is basically a diagnosis of exclusion, patients were submitted to several tests. It is essential to exclude mainly infectious and other auto-immunes diseases, so viral serological markers (cytomegalovirus, hantavirus, hepatits B virus antigen, Epstein-barr virus, herpes simplex virus, syphilis, streptococci, tuberculosis, toxoplasmosis, brucellosis, rubella, salmonella); blood cultures; tests for rheumatoid arthritis factor; Coombs' reaction; and also immune complexes/immunologic markers (antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), anti-ds DNA, Anti SSA/Ro, Anti SSB/La, serum IgG4 levels, PPD skin testes, serum angiotensin-converting enzyme level, complement and anti- streptolysin O antibody titers) to exclude diseases such as Sjogren's syndrome, sarcoidosis, systemic lupus erythematosus, granulomatosis with polyangiitis, Behçet's syndrome and IgG4-related autoimmune diseases were routinely performed.

SYSTEMIC IMMUNOSUPPRESSION

The fact that patients with TINU respond very well to immunosuppression also favors the auto-immune hypothesis. There is no standard treatment for TINU syndrome; some clinicians prefer a "wait and see" strategy, while others, in order to control patients' symptoms, favor treatment. Nephritis in TINU syndrome is usually self-limited. However, inflammation maintained over time can cause fibrosis and chronic kidney failure (CKF). For this reason, patients are treated with systemic corticosteroid therapy for a period of 3–6 months, normalizing laboratory parameters in most patients.[77]

In general, patients respond favorably to corticotherapy, however further studies are needed to determine which steroid is the most adequate, its duration and posology, in order to not submit patients to unnecessary medication, the association between the treatment carried out with time free from illness, would also be important. According to Legendre et al patients receiving corticosteroids had greater percentage of improvement in serum creatinine levels and estimated glomerular filtration rate, than those without corticosteroids. Moreover, oral corticosteroids were associated with a smaller number of recurrences of uveitis.[12]

Others systemic immunosuppressors, such as methotrexate, mycophenolate mofetil, azathioprine, cyclophosphamide, and cyclosporine A, also play an important role in TINU treatment, more specifically during recurrence in patients cortico-dependents, cortico-resistant's or with contra-indications for corticotherapy.[17,21,38, 44,47,52]

RELAPSE

Relatively to treatment, although most patients responded to corticosteroids, the posology and treatment duration remains an open question for debate. Since the patients follow up time was different between the series, there may be a bias of follow up. Nonetheless the estimate of 48.3% of relapses makes it important to determine the cause, possibly between an inadequate dosage or an immunosuppressor drug. It would be important to study predictive factors between clinical analyses, renal histology and ocular findings for the need to medicate with immunosuppressants.

POTENTIAL BIOMARKERS

Biomarkers are entities such as cells, molecules, genes, enzymes or hormones that can be measured experimentally and indicate the occurrence of a pathological function of/on the organism. They can be obtained relatively easily from bodily fluids and can be used in clinical practice for diagnosis, as risk factors for the occurrence evaluation, to stratify patients and identify the severity or progression of TINU syndrome. Moreover, they can predict prognosis or monitor a particular treatment so that some side effects are less likely to occur.

Tan *et al*[18] investigated the potential role of IgG autoantibodies against modified C-reactive protein (mCRP), given its high prevalence, in patients with TINU syndrome, especially in the active phase of nephritis. They found that the anti-mCRP autoantibodies might bind to overexpressed mCRP in renal and ocular tissues and thus may induce subsequent renal and eye injury. Therefore, it might be a target autoantigen, requiring however additional study to evaluate its possible use as a serologic biomarker in the clinic. On the same work field, Li *et al* reported that patients diagnosed with drug-induced acute tubulointerstitial nephritis, who went on to develop late-onset uveitis, had higher levels of mCRP-Ab compared with those who had true drug-induced acute tubulointerstitial nephritis, revealing that an elevated mCRP-Ab level (>20.2%) at biopsy would serve as an independent risk factor for late-onset uveitis and could discriminated late-uveitis TINU from drug-induced acute tubulointerstitial nephritis.[17]

Sugiyama *et al*,[36] searched for urinary biomarkers. It is known that during renal parenchymal inflammation in humans, neutrophil gelatinase-associated lipocalin (NGAL) protein accumulates in the renal proximal and distal tubules,[78] showing the largest fold increase and the quickest response to treatment compared with other traditional urinary biomarkers in interstitial nephritis concluding that NGAL may be the most sensitive biomarker during glucocorticoid treatment.[79] Urinary L-type fatty acid binding protein (L-FABP) found in the cytoplasm of human proximal tubules, has a high affinity and capacity to bind long-chain fatty acid oxidation products, and may have a protective effect on damaged proximal tubules[80]; however, in their study, urinary L-FABP levels decreased gradually compared with other biomarkers and may not indicate precise activity in this syndrome.

Kanno *et al*[11] evaluated the role of urinary abnormalities, as altered urinary β2-microglobulin and serum creatinine, as a potential indicator for diagnosis, all (100%) patients had increased urinary β2-microglobulin but only 40% had increased serum creatinine. Urinary β2-microglobulin is a very sensitive marker for tubular damage, and its analysis is helpful in the diagnosis of TINU syndrome,[2,3,19] especially when a renal biopsy is not indicated, as verified by Giralt *et al*[75] that within their study population, 85.4% presented with elevated urinary β2-microglobulin. On the other hand, Choi *et al*[23] affirm that since renal disease is transient, urinary β2-microglobulin and serum creatinine may no longer be elevated by the time a suspected patient is seen by an ophthalmologist, meaning that it is very important to take into consideration the duration of symptoms and patients medical history. Provencher *et al*[24] also concluded that urinary β2-microglobulin correlates with uveitis activity and trend down over the course of TINU. Therefore, may serve as a useful tool in determining where patients are in their systemic disease course, reporting that Uβ2M levels also correlate strongly with the activity of ocular inflammation, this correlation tends to be stronger than that of SCr.

Hettinga *et al*[19] searched for predictive value of urinary β2-microglobulin, urinary protein, and serum creatinine in detecting TINU syndrome in young patients with uveitis and observed that urinary β2-microglobulin and serum creatinine levels are a sensitive and relatively simple diagnostic screening tool for detecting renal dysfunction to diagnose TINU syndrome in young patients with uveitis.

Therefore, it is a possible clinic tool to use in patients with idiopathic uveitis in order not to miss a diagnosis of TINU, being that, in most cases, determinant of renal prognosis.

Hayashi *et al*[13] developed a long-term observation of kidney function normalization and found an association between higher urinary β2-microglobulin / creatinine (>2000 μg/g Cr) at diagnosis and longer duration for normalization of kidney function and longer treatment period for uveitis, recognizing the need for an extended follow up period.

Regarding study limitations, the majority of studies in this review are case reports, therefore both the inability to generalize the results, since it is not population representative, and its retrospective nature, as well as case series, it can lack important information, for example, lack of follow-up time or specifies regarding patients' treatment or approach. Furthermore, we were not able to include several articles since they were either written in foreign languages or full text was not available, which may have omitted significant studies.

In conclusion, diagnosis of TINU syndrome is growing, along with age at presentation, due to general awareness for this clinical entity. Although presentation can be variable, TIN typically presents first, with systemic symptoms such as fatigue and uveitis, is, by far, anterior and bilateral. Corticosteroids seem to be the best first-line treatment available with, mycophenolate mofetil and azathioprine remaining as good alternatives, especially in cases of resistance or impossibility of using steroids. Despite the relapses, the prognosis was generally favorable.

It is also consensual that data from larger studies are necessary in order to have a stronger association, regarding genetic predisposition, inflammatory mediators, and potential biomarkers.

ACKNOWLEDGMENTS

I would like to express my sincere gratitude and dedicate this work to all of those who helped me in this stage and contributed to its accomplishment.

A special gratitude to Dr. Alberto Paulo Campos Freitas da Costa, for whom I have great admiration and I am grateful for all the commitment, availability, collaboration, advice, scientific and methodological teachings throughout the completion of this dissertation. I would also like to thank the co-supervisor Prof. Doctor Luís Pedro Caldas Figueira for his support, advice, collaboration, and availability.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

All authors contributed to the study conception.

Joana Pereira: bibliographical search, data collection, analysis and interpretation of results, drafting of the article.

Paulo Freitas-da-Costa and Luís Figueira: analysis and interpretation of results, critical reviewing of the content of the article.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram não possuir conflitos de interesse.

Suporte Financeiro: O presente trabalho não foi suportado por nenhum subsidio o bolsa ou bolsa.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

ETHICAL DISCLOSURES

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financial Support: This work has not received any contribution grant or scholarship.

Provenance and Peer Review: Not commissioned; externally peer reviewed.

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